REMARKS

After amending the claims as set forth above, claims 21, 24-40, 43, 50, 54-63, 69-80 , 101 and 102 will be pending in this application. All other claims have been cancelled.

Claim 21, which is one of two independent claim in the case, is directed to plants that contain plant cells that express a non-plant biologically functional multimeric protein resulting from assembly of at least two different polypeptides. According to the method, the plant cells contain nucleic acid encoding the two different polypeptides each including a leader sequence which forms a secretion signal for individual polypeptide. As discovered by the inventors, proper processing of the each polypeptide is required so that the two polypeptides can form a biologically functional multimeric protein. Claim 43, which is the second independent claim in the case is similar to claim 21 except that the two different polypeptides are the heavy and light chain of an antigen specific immunoglobulin.

Applicant has amended claim 21 to reinstate subpart "b)" which was inadvertently deleted during the last response. Claims 69 and 80 have been amended herein and new claims 101-102 newly added. The amendments are supported by the specification and raise no issue of new matter.

The specification has been amended to update related application data. This amendment raises no issue of new matter.

REQUEST TO CORRECT INVENTORSHIP

A request to correct inventorship under 37 C.F.R. § 1.48(b) was previously filed along with the Request for Continued Examination. However, the Office Action of February 10, 2003, does not indicate whether or not the request was granted or even acted upon. Applicant requests that the examiner indicate in the next action whether

inventorship will be changed in accordance with the request. If the request has been lost, the examiner is urged to contact the undersigned for a replacement copy.

UPDATING RELATED APPLICATION DATA

Applicant has amended the specification on page 1 to update related application data in accordance with the PTO's waiver of 37 C.F.R. 1.121 (a)-(d).

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The rejection of claim 21 as being allegedly indefinite for reciting "(a)" as only a single subpart has been obviated by the addition of subpart "(b)." Accordingly, withdrawal of the rejection is respectfully requested.

The rejection of claim 69 as being allegedly indefinite for the recitation of "wherein the immunoglobulin heavy chain is selected from the group consisting of IgA, IgD, IgE, IgG and IgM" has been obviated by amendment herein. Accordingly, withdrawal of the rejection is respectfully requested.

The rejection of Claim 80 under 35 U.S.C. § 112, second paragraph as being allegedly indefinite because "derived" is unclear as to "what would be retained by the plant of claim 21 from which the plant cell is "derived", is respectfully traversed. It is noted that there is no basis given for why this term is unclear. A plant cell obtained from a plant is one that is derived from the plant as derivation means to "[t]o obtain or receive from a source." (first definition of derived under www.yourdictionary.com). Thus, there is nothing indefinite about "derived" in claim 80.

However, Applicant has amended claim 80 to further prosecution of the case. Derivation of a plant cell from a plant is the same as obtaining a plant cell from a plant. Accordingly, withdrawal of the rejection is respectfully requested.

REJECTION UNDER 35 U.S.C. § 102 OVER DÜRING

The rejection of claims 21, 24-26, 29-39, 43 and 54-61 under 35 U.S.C. § 102(b) as being allegedly anticipated by the During Dissertation is respectfully traversed. The Office Action states that the basis for the rejection is set forth in the Office Action mailed August 28, 2001. In that action, the examiner asserted that During is enabling and that Applicant's arguments did not meet the burden of establishing non-enablement of the During Dissertation. The current Office Action acknowledges Applicant's filing of a rule 132 declaration by Richard Lerner addressing various deficiencies of the During Dissertation. However, it appears that the examiner has discounted the significance of Lerner's various analyses on the alleged basis that the claims are not commensurate in scope. See Office Action, page 6. More specific arguments relating to Lerner appear at the top of page 7 of the Office Action. One asserts that During's assay sensitivity and lack of controls are not germane, while another asserts that post publication of During's work in the journal Plant Molecular Biology constitutes evidence supporting enablement. Each of these three allegations are addressed below.

1) **The claims are commensurate in scope with Applicant's arguments and analyses of the Lerner declaration**

Claim 21 as currently amended includes subpart "(b" which requires biologically functional multimeric protein encoded by the nucleotide sequences non-native to the cell. Also expressly required is for the biologically functional multimeric protein to result from assembly of the encoded polypeptides. Thus, it can no longer be argued that claim 21 is not commensurate in scope with Applicant's arguments relating to the Lerner declaration.

Furthermore, the examiner's attention is drawn to independent claim 43, which at the time of the last Office Action, was directed to expression of immunoglobulin in plant cells and included a requirement for heavy and light chain production, processing, and assembly into a antigen-specific immunoglobulin. The position taken by the Office Action that the claims are not commensurate in scope with Applicant's arguments and the Lerner declaration is wholly inapplicable to claim 43.

In fact, as was noted previously by Applicant (Amendment of 1/28/02) claim 43 contains language similar to claim 21 of copending 09/199,534, now issued as U.S. Patent No. 6,417,429. U.S. Patent no. 6,417,429, issued over the Düring Dissertation and the Goodman patent. As was argued successfully in copending 09/199,534, neither Düring or Goodman, alone or in combination failed to anticipate or render obvious a plant cell that contains nucleic acid sequence encoding an immunoglobulin light and heavy chain each with a leader sequence and contains immunoglobulin molecules where the leader sequences are removed following proteolytic processing in the cell.

2) The Lerner declaration establishes that the During Dissertation does not enable expression in plants of functional multimeric protein not normally produced in plants.

It is Applicant's position that one skilled in the art would have reasonably doubted During's assertion that he successfully expressed an antigen specific immunoglobulin in plants.

a) Lerner establishes the existence of a prejudice in the art against expressing an antigen specific immunoglobulin in plants

Applicant supports this conclusion with the Lerner Declaration previously of record in this case. Lerner addresses the view of the skilled artisan in the proper timeframe, the period beginning from the alleged publication date of the During dissertation (July 1988) and up to the earliest filing date of the above captioned patent application (October 27, 1989). His analysis shows that there is strong evidence at the relevant time period for the existence of a prejudice in the art against the possibility of using plant cells to process and assemble an antigen-specific immunoglobulin. According to Lerner, it was appreciated by the early 1980s that the biology of antibody expression was complex and varied with the maturation state of the B cell. For example, rearrangement of immunoglobulin chain variable region encoding gene segments is required to form a functional immunoglobulin gene, and rearrangement of the heavy chain occurs before rearrangement of the light chain. In fact, there is an early stage B cell known as the "pre-B cell," characterized in

having a productively rearranged heavy chain V gene but not a rearranged light chain V gene. Lerner declaration, ¶3. In contrast, a later stage of B cells is known (i.e., "young B cell), characterized in having both the heavy and the light chain V genes productively rearranged and in expressing a full-sized immunoglobulin on the cell surface. *Id.*

Lerner goes on to explain that antibody expression in B cells was understood to be further complicated by the involvement of the BiP protein, known to be involved in heavy chain processing. Lerner declaration, ¶3. A phenomenon called heavy chain toxicity also was appreciated at the time but its mechanism was unknown. Lerner declaration, ¶4. According to Lerner, by the mid 1980s, a prejudice had taken hold in the art against the notion that antigen-specific immunoglobulins could be produced in cells other than mammalian B cells. *Id.*

Although Lerner notes the existence of reports describing expression of an assembled antibody in two microorganisms (i.e., *Saccharomyces cerevisiae* and *E. coli*) he provides substantial reasoning for why the prevailing prejudice in the art would still have existed with respect to producing antigen-specific immunoglobulin in plant cells. Lerner declaration, ¶7. For example, Lerner notes that plant cells were known to be different from mammalian cells and from microorganisms such as *Saccharomyces cerevisiae* and *E. coli* not only in having a cell wall but also in features related to protein secretion. In addition, Lerner notes that it was not known at the time whether plant cells contained a BiP protein or a functionally equivalent analogue. Lerner concludes from his review of the field that:

> [T]here was a sound basis for a real prejudice in the art against using plants to produce a processed and assembled immunoglobulin which is antigen specific around the time of the During dissertation (*circa* 1988/1989). Were this not the case, then Applicant's invention clearly would not have been roundly hailed in both the scientific literature and in the general press as a significant scientific discovery and medical breakthrough.

Lerner declaration, ¶8 (footnotes removed).

Applicant has established, therefore, through the Lerner Declaration, the existence of a prejudice in the art against using plants to express antigen-specific immunogloblin by *in situ* processing of the signal sequence and assembly of the heavy and light chains. This prejudice is relevant to the pending claims and requires that the teachings of the During declaration must be viewed in light of this prejudice. **It is noted that the only rebuttal to this conclusion in the Office Action is the allegation that the claims are not commensurate with this conclusion, a position no longer tenable as addressed above.**

b) During's conclusion to have expressed antigen specific immunoglobulin in plants is based on insufficient experimental proof

During initially made a light chain only expression vector and evaluated whether plant cells transfected with this vector could express light chains. During, however, failed to detect light chain production in the cells (During dissertation, p. 80, line 2). According to Lerner, this fact would have been disturbing to the ordinary skilled artisan because light chain alone is readily expressed in B cells, and even if During's cells were making a small amount of light chain, albeit at a level below his detectability limit, this would complicate efforts to achieve and detect heavy-light chain assembly. The Lerner Declaration further points out that an increased relative heavy chain expression, which under the circumstances might be necessary to obtain assembly in view of the low levels of expressed light chain, conceivably could result in toxicity if plant cells were susceptible to heavy chain toxicity, as was the case for mammalian B cells. These issues would have raised serious questions about During's chances for success and would have required additional proof for any alleged success to be accepted in the art.

Although During appreciated that his expression system was suboptimal, he proceeded to attempt expression of both a heavy and light chain from a single expression vector. Anticipating a threshold detectability problem, During utilized a pre-enrichment step prior to Western blotting (i.e., indirect Western) of transgenic plant extracts. Lerner declaration, ¶14. Lerner points out that During's need for an indirect Western also would have been disturbing to the ordinary skilled artisan because direct Western blotting was

known to be a very sensitive technique that had previously been successfully used to demonstrate foreign host expression (including plant expression of antibodies as disclosed in the instant patent application). *Id.*

The Examiner is referred to the Lerner declaration § 15 for details of During's indirect Western results. It is significant that During now observed light chain detection with the dual chain vector (but not with the light only vector used earlier) but was unable to detect heavy chains by either direct or indirect Western blotting. *Id.* **During's assertion that he has detected the presence of assembled B1-8 antibody in the plant cells is based, according to Lerner, on faulty circular logic.**

> To conclude as he does from the Western results that assembled B1-8 antibody was present in the plant extract, During must infer that which he is attempting to prove, that fully assembled antibody must have been present in the extract for light chain to have been enriched following binding to the NP hapten immunoabsorbent. As will be seen below, this faulty circular reasoning is open to alternative explanations that directly conflict with During's conclusion.

Lerner declaration, ¶ 15. Lerner goes on to discuss numerous other reasonable explanations for the results that During did not address, let alone attempt to exclude. Notably, During fails to exclude the real possibility that light chain may have been enriched by the NP immunoabsorbent even if the light chain were not assembled with a heavy chain. During's failure to detect heavy chains by direct and indirect Western blotting is consistent with this possibility. As summarized by Lerner, there was much that During could have done (but failed to do) to exclude alternative artifactual explanations for his Western blotting data.

> For example, During could have directly demonstrated that heavy chain was absolutely required for light chain binding during the pre-enrichment step. Alternatively, or in addition, During could have used biosynthetic radiolabeling of plant cells in combination with Western blotting to prove that a heavy chain was in fact co-enriched with light chain. This method is well known in the art and was previously used to demonstrate foreign protein expression. Biosynthetic radiolabeling also helps to control for stripping of antibody during a low pH

> elution of an antibody immunoabsorbent column (i.e., the Ls136 adsorbent), a problem encountered with CNBr. Since During employed low pH elution and CNBr linkage, he should have provided controls to address this potential problem.

Lerner declaration, ¶ 16 (footnotes removed).

The During dissertation also evaluated antibody expression in his plants using a second technique referred to as "tissue printing." In this technique, a leaf is pressed against a membrane in order to bind proteins in the leaf to the membrane, and the membrane is probed by immunological reagents as in Western blotting. The During dissertation describes that light chain, heavy chain and "aggregated B1-8" antibody were detected by tissue printing. Although During asserts that these results support his conclusion of successful immunoglobulin assembly, **Lerner believes that the tissue printing xperiment are just as readily subject to alternative explanations because they lack controls which are essential to conclude that binding of an immunological reagent is antigen-specific**. Lerner declaration, ¶ 17. Lerner bases his belief not only on his own experience as a scientist and immunologist for more than 30 years but also on the scientific literature. With respect to the latter, Lerner points out that the types of controls lacking in the During dissertation were used by others who previous to During demonstrated expression in yeast of the same B1-8 antibody that During was attempting to express in a plant. *Id.* (referring to Wood et al.) The few controls used by During in the tissue printing experiments were wholly insufficient under the circumstances to support During's assertion of success.

The During dissertation also includes immunogold electron microscopic analysis of his transgenic plant cells apparently with the same antibodies used in the Western blotting and tissue printing experiments. The Examiner is referred to the Lerner declaration § 18 for a detailed explanation of During's immunogold results. Lerner takes issue with During's conclusion that the immunogold results indicate successful assembly of the B1-8 antibody in plants. **First, Lerner notes that the heavy chain again was not detected. In addition, Lerner points ut that th areas f the cell that were immunog ld lab led with the light chain reagent were not th same areas that were immunogold labeled with the**

Ac38 reagent (alleg dly specific f r an assembled B1-8 heavy and light chain). Lerner declaration, ¶ 18. It stands to reason that for assembly to have occurred, the two chains should be co-localized to at least one area of the cell. Furthermore, During failed to observe immunogold labeling in regions of the cell that one would normally have expected if antibody assembly were possible in plant cells. Lerner declaration, ¶ 19. Indeed, During observed immunoreactivity inexplicably in chloroplasts with the Ac38 antibody but not in the golgi apparatus or vesicles as others have observed previously for secreted proteins, including antibodies. According to Lerner, unusual results might be acceptable if plant cells were capable of antibody assembly in unique and previously unknown ways, however, unusual results cannot make up for the lack of controls in other experiments.

The Lerner Declaration concludes that a person skilled in the art of immunology or protein expression, circa 1988/1989, would not have reasonably believed the assertion of the During dissertation that plant cells could be used to process and assemble an antigen-specific immunoglobulin. Lerner declaration, ¶ 22. Lerner bases this belief on During's failure to perform critical controls to support his conclusions and to explain his inconsistent results. Also, the Ac38 antibody which underlies virtually all of the support for During's assertion cannot be used, according to Lerner, to prove that NP antigen specific binding was present in transgenic plant cells. Lerner declaration, ¶ 22.

To summarize, Lerner identified the following experimental deficiencies with the During Dissertation:

1. Faulty circular logic was employed to prove the existence of the B1-8 antibody

2. Critical controls were not used allowing for artifactual explanations.

3. Heavy chain could not be detected.

4. Immunogold labeling was contradictory and inconsistent with what was known about antibody processing and assembly.

c) The experimental deficiencies of the During Dissertation are relevant to the question of enablement

It is noted The Office Action contains nothing that rebuts the specific finding or conclusions of the Lerner Declaration. The examiner, however, comments to a limited extent on the significance of Lerner's findings to Applicant's arguments (Office Action, page 7).

> Furthermore, that During required extremely sensitive assays to detect the presence of antibodies or did not include certain controls is also not germane absent evidence that During's assays could not have detected expressed antibodies.

The four deficiencies summarized above, including use of faulty circular logic, absence of critical controls, failure to detect the heavy chain, and inconsistent and inexplicable results by immunogold staining all go to the critical question of what was actually detected by During in his assay. It is respectfully submitted that absence of critical controls is germane to whether During's assay could have detected the expressed antibodies. During's use of faulty circular logic, failure to detect the heavy chain, and inconsistent and inexplicable results by immunogold staining are similarly germane to the question of what his assay was detecting.

d) The 1990 publication by During does not remedy the deficiencies of his dissertation

The examiner considers During's 1990 publication in the journal Plant Molecular Biology as evidence supporting enablement of the During dissertation (Office Action, page 7) and appears to be using the publication to discount the conclusions of the Lerner declaration that During's dissertation work would not have been considered convincing when it was first published (allegedly in the 1988 time frame). It is respectively submitted that the 1990 Plant Molecular Biology publication is deserving of little if any weight in this regard for the following reasons.

i. **Ther ar content differenc s betw n the Plant M lecular Biol gy publication and the diss rtati n**

During's 1990 publication in Plant Molecular Biology does not include the same results as the dissertation. In particular, there is no mention in the 1990 publication of During's failed attempt to detect expression of the light chain from his initial vector which did not include a heavy chain. The relevance of these experiments to During's overall conclusion was addressed by Richard Lerner whose comments on the matter are reproduced below for the convenience of the examiner.

> The During dissertation describes that plant cells were initially transfected with DNA encoding the antibody light chain but not the heavy chain. Incredibly, During was unable to detect light chain in the cells. The failure to detect expression of light chains would, in my opinion, have been disturbing to the ordinary skilled artisan because it was known that light chains can be readily expressed without heavy chains in B cells. In addition, a very low level of light chain expression would make it that much more difficult to detect heavy-light chain assembly. Furthermore, an increased relative heavy chain expression, which under the circumstances might be necessary to achieve assembly in view of the low levels of expressed light chain, conceivably could result in toxicity if plant cells turned out to be susceptible to heavy chain toxicity as is the case for B cells. Thus, During's failure to detect light chain expression in cells transformed to express only the light chain would have raised serious complicating issues requiring a more thorough investigation.

Lerner declaration ¶ 13 (footnotes removed). There can be do doubt that Lerner believed these failed experiments to be significant to the overall conclusions of During and that they would have raised serious about the ultimate believability of During's work.

ii. **The relevant knowledge in the art was very different at the time of the dissertation versus when the submission to Plant Molecular Biology was under peer review**

Various facts support that the state of the art at the time when During's 1990 article was under review was much different from when the 1988 dissertation was published. Although the During dissertation was allegedly published sometime in 1988, a

draft of the scientific article that was eventually published in Plant Molecular Biology indicates that it was not submitted for review until November 14, 1989. Thus, about a year or more elapsed between the time the dissertation was published and the work was submitted for peer-review.

The inventors, Hiatt and Hein, published their work with great fanfare in the prestigious journal Nature on November 2, 1989. The Nature publication included an article by the inventors and featured the inventors' work on the cover page of the journal. An article about the inventors' work was also published that same day in The Los Angles Times. (Both publications may be found in appendix 14 of the Lerner declaration). It is respectfully submitted that the state of the art with respect to expressing heteromultimeric proteins such as immunoglobulins in plants changed signficantly as of November 2, 1989. According to Richard Lerner, the prejudice in the art against using plants to express antigen-specific immunoglobulin was removed by publication and acceptance of inventors's work, and not by During's dissertation.

> I am convinced that the ability to process, assemble, and secrete antigen specific immunoglobulin in plants was not achieved prior to the disclosure by Hiatt *et al.*, (see, e.g., article in Nature and in U.S. Patent No. 5,202,422). The inventors used a different strategy from During and achieved a significant level of expression, allowing detection of the assembled chains by direct Western blotting. Hiatt et al., not During, was the first to convincingly demonstrate the ability of plants to support production of an antigen-specific immunoglobulin in a manner that overcomes the prejudice in the art.

Lerner declaration, ¶ 23 (footnotes deleted).

The facts show that it was only after the inventor's went public with their ground breaking discovery and changed the view of the scientific community that During came forward and submitted his work for peer-review. The 1990 Plant Molecular Biology publication indicates a date of submission of November 14, 1989, nearly two weeks after public disclosure by the inventors, Hiatt and Hein. It is unclear why During waited a year or more after the dissertation to submit his work for peer-review. Considering the

potential significance of the findings, one would have expected a rush to publication rather than a delay, unless of course, the author doubted the accuracy of the work or was concerned that it would not pass peer-review under the then present state of knowledge.

The facts also support that any reviewer almost certainly would have known of the inventor's work when reviewing During's submission to Plant Molecular Biology. As indicated in the 1990 publication, review of the article was not completed until May 1990, nearly six months after the November 1989 publication by Hiatt and Hein. This would have provided ample time for a reviewer to become familiar with Hiatt and Hein's work. In fact, in March of 1990, Hiatt published an additional article on plant expression of antibodies in Nature. Hiatt, Nature, (1990 March) 29;344(6265):469-70; (attached as EXHIBIT 1). Thus, there were two separate publications of the inventor's work in the prestigious journal Nature before the review of During's submission to Plant Molecular Biology was complete. Furthermore, During actually discusses Hiatt and Hein's work in his Plant Molecular Biology submission (see page 291, right hand column). All of these facts make it very unlikely that a reviewer would not know of the inventors' work and its impact on relevant knowledge in the art.

iii. **Differences in the content of the submission and in the state of the art at the time of review necessitates a conclusion that the 1990 publication does not support enablement of the During dissertation**

The ultimate publication by During in Plant Molecular Biology nearly two years after his dissertation should be given little if any weight to the question whether the During's dissertation is enabling. This conclusion is based on a significant change in the content of the 1990 publication versus the earlier dissertation and on the fact that review of During's 1990 publication occurred in the light of a very different scientific climate, where the prejudice in the art had been removed by publication of the inventors's work. Clearly, the effect of removing failed experiments would be to cast the later work in a better light when exposed to peer-review. The modified content of During's 1990 journal submission must also be viewed in light of the much changed state of the art resulting from

publication of the inventors' work. Both these facts (changed content and state of the art), not applicable to the dissertation, worked in favor of publication. Thus, it is not proper to use During's publication in Plant Molecular Biology as evidence that During's earlier dissertation was enabling. As was discussed by Lerner, publication by the inventors Hiatt and Hein paved the way for later acceptance of During's work.

> In my opinion, During's antibody experiments would not have been published were they not supported by the earlier published success of inventors, Hiatt and Hein. Had During attempted to publish his work in a peer reviewed journal before Hiatt and Hein published their work, my extensive experience as a reviewer/editor of scientific journals leads me to conclude During's work would most likely have been rejected as inconclusive.

Lerner declaration, ¶ 22. Thus, it is respectfully submitted that the ability of the 1990 publication to support enablement of the 1990 dissertation is severely undercut by differences in these two documents and by the much increased knowledge in state of the art owing to the work of the inventors, not that of During.

It is respectfully submitted, therefore that all of the above demonstrates that the During dissertation fails to provide an enabling disclosure that teaches the elements of claim 21 and 43 and their dependent claims including the requirement for the multimeric protein to have a leader sequence for each polypeptide that forms a secretion signal which is cleaved following proteolytic processing, and the requirement for assembly of the polypeptides in the plant cell resulting in formation of a multimer which is a biologically functional non-plant hetero multimer (i.e., "antigen-specific," in the case of immunoglobulin). Accordingly, because the During dissertation fails to provide an enabling disclosure, the claims are not anticipated under section 102(b) as a matter of law.

REJECTION UNDER 35 U.S.C. § 102 OVER GOODMAN

The rejection of claims 21, 24-27, 29-40, 43, 54-62, 69-72, 76, 77 and 79-80 under 35 U.S.C. § 102(e) as being allegedly anticipated by Goodman (U.S. No. 4,956,282) is respectfully traversed. In that Office Action, it was asserted that Goodman teaches plant expression of "interferon (homomultimer), enzymes and immunoglobulin heavy and light chains (heteromultimer)." It was asserted that absent evidence to the contrary, Goodman was considered an enabling disclosure for all that is asserted therein.

Two additional arguments were included in the last Office Action. 1) In response to Applicant's argument that Goodman is limited to teaching the production of gamma interferon in plants, the examiner countered that the rejected claims are not limited to immunoglobulin multimers (page 8). However, it is respectively submitted that claim 43 and its dependent claims are limited to immunoglobulin multimers. Thus, the examiner's rebuttal fails with respect to the these claims. Furthermore, claim 21 and its dependent claims cover heteromultimeric proteins. Such proteins exclude interferon, which the examiner admits to be homomultimeric. Thus, the examiner's rebuttal is also irrelevant to claim 21 and its dependent claims.

In response to Applicant's argument that Goodman is not enabling because it does not address any of the factors that one should consider when attempting to obtain assembly of a functional multimeric protein, the examiner countered with a new rebuttal that the claims do not require assembly or presence of a functional multimeric protein in plant cells nor do they recite the function that the assembled multimeric proteins would exhibit. Applicant has amended claim 21 to include a part "(b), inadvertently deleted from the last response, which requires assembly of a functional multimeric protein in plant cells. As the asserted basis for sustaining the rejection has been addressed, the rejection should be withdrawn. In the case of claim 43 and dependents, the examiner apparently overlooked the fact that these claims included a requirement for assembly of a heavy and light chain to form an antigen specific immunoglobulin. Thus, the asserted new rebuttal is not applicable to these claims.

Furthermore, Applicant maintains that Goodman is not an enabling reference with respect to any pending claim. As already discussed, the meager disclosure in Goodman (col. 1, lines 62 to col. 2 line 7) that must enable expressing any non-plant heteromultimer in a plant fails to discuss any of the factors that one should be aware of when attempting to obtain assembly of a functional multimeric protein. These factors include, for example,: 1) Methods for introducing the nucleic acid sequences encoding each of the polypeptides into the same host cell. Goodman is silent as to methods for co-transformation of multiple vectors or vectors containing more than one coding nucleic acid sequence; 2) Equivalent expression of each polypeptide chain, produced in sufficient concentration, in the same cellular compartment. Goodman fails to teach transcriptional and translational requirements for expressing multimeric proteins, such requirements being significantly different from the requirements for expressing a single polypeptide. For instance, the promoters operatively linked to the nucleic acid sequences should insure that mRNA expression occurs at the same level; 3) Each polypeptide should have a functional leader sequence which is processed along the protein secretory pathway via proteolytic cleavage; and 4) Methods which allow the regeneration the transformed cell in a manner that ensures that both genes are retained during the process. In view of these and other deficiencies, the mere mention to express a multimer such as an immunoglobulin in Goodman amounts to nothing more than an invitation to experiment. There can be no doubt that Goodman falls far short of overcoming the perceived prejudice in the art against expressing immunoglobulins in plants, as described in the Lerner declaration and discussed extensively above under the rejection for anticipation over During.

Applicant's position that Goodman does not enable expression of any non-plant heteromultimeric protein in plants finds additional support from the file history of the Goodman patent, which issued from U.S. application serial no. 760,236 filed July 29, 1985. Claim 1 of 760,236 broadly drawn to a "method for producing a mammalian peptide" is limited to expressing a single mammalian polypeptide. Original claims of 760,236 are attached as EXHIBIT 2. Thus, the originally filed claims indicate that Goodman never seriously considered that his discovery could be extended to

heteromultimeric proteins. Furthermore, the Patent Office rejected originally filed claim 1 and other claims of the Goodman application as being nonenabled.

> Claims `1-5, 7, 8, 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to Agrobacterium-mediated dicot transformation with chimeric genes comprising opine synthase promoters and structural genes encoding human interferon or antibiotic resistance as per pages 10-18. . . . Given the unpredictability inherent in the art, undue experimentation would be required by one of ordinary skill in the art to determine DNA sequences for non-disclosed mammalian peptides or promoters and to develop transformation vectors resulting in detectable expression of stable, bioactive peptides as claimed in claims 1-5, 8, 10 and 11.

U.S. serial No. 760,236, Office Action 6/9/87, pages 3-4 (Office Action attached as EXHIBIT 3). Goodman failed repeatedly to convince the examiner to withdraw the rejection over enablement and eventually appealed the case to the Board of Patent Appeals and Interferences. On September 29, `1989, the Board affirmed the rejection for non-enablement. The Board's decision makes clear that the patent is not enabling for any mammalian peptide other than interferon.

> It appears to have been accepted by the examiner that the experimental portion of appellants' specifcation enables one of ordinary skill in the relevant art to repeat that which appellants have done, i.e., obtain the expression of an interferon gene through the use of a transformed Ti-plasmid in dicotyledonous plant cells. In view of the very same high order unpredictability of success in extrapolating reported procedures to different systems, e.g., different genes, different vectors, and different hosts, discussed above, appellants' arguments that their disclosure enables one of ordinary skill to practice the inventions claimed more generally in the broader claims without the exercise of undue experimentation are unreasonable on their face.

BPAI Decision, page 4-5 (BPAI decision attached as EXHIBIT 4).

The position of the examiner in the instant case that Goodman is enabling for the expression in plants of any non-plant heteromultimeric protein is clearly in conflict with the Patent Office's earlier position during prosecution of the Goodman that the specification is enabling only for interferon. Goodman never even bothered to assert claims that would cover expressing heteromultimeric protein and the decision of the Board of Patent Appeals and Interferences leaves no doubt that the Goodman specification would not have been adjudged to enable expressing heteromutimeric proteins. It is respectfully submitted that the examiner's position in the instant case that Goodman enables expression of any non-plant heteromultimeric protein in plants is without basis for the reasons discussed above and in conflict with earlier decisions of the Patent Office.

However, even if one were to conclude that the Patent Office was wrong in limiting Goodman solely to expressing interferon, it is another thing entirely to extend Goodman to heteromultimeric proteins in view of the absence of even minimal disclosure needed for this endeavor as discussed above. Furthermore, During's dissertation work on antibody expression several years later, which was fraught with problems and would not have been convincing to one skilled in the art, argues against taking Goodman's disclosure beyond single polypeptide expression to heteomultimeric protein expression.

Thus, it is respectfully submitted that Goodman is not enabling for any of three reasons discussed above. The examiner, therefore, is respectfully urged to withdraw the rejection of the claims as anticipated by Goodman.

REJECTION UNDER 35 U.S.C. § 103 OVER DÜRING

The rejection of claims 21, 24-40, 43, 50, 54-63 and 69-80 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Düring in view of "Applicant's allegedly admitted prior art for the reasons of record set forth in the office action mailed August 28, 2001" is respectively traversed.

At the outset, Applicant wishes to address the assertion that the rejection over During is based "Applicant's allegedly admitted prior art for the reasons of record set forth in the office action mailed August 28, 2001." First, it is unclear what is being referred to

as "Applicant's allegedly admitted prior art." Applicant is not aware of any admitted prior art and requests that the examiner specify any such art and indicate if and how it is being relied upon in any subsequent rejection.

The instant obviousness rejection appears to be the identical or nearly identical to the rejection for anticipation over During. As the obviousness rejection mentions no specific art to be combined with During and raises no issues beyond those discussed under the rejection for anticipation, the examiner is referred to Applicant's rebuttal of During under anticipation for Applicant's rebuttal under obviousness. It is respectfully submitted that During is not enabling with respect to any pending claim and this deficiency is not remedied by any reference of record in the case.

REJECTION UNDER 35 U.S.C. § 103 OVER GOODMAN

The rejection of claims 21, 24-40, 43, 50, 54-63, and 69-80 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Goodman for the reasons set forth in the Office Action mailed August 28, 2001, is respectively traversed.

At the outset, Applicant wishes to address the assertion that the rejection over Goodman is based "Applicant's allegedly admitted prior art for the reasons of record set forth in the office action mailed August 28, 2001." First, it is unclear what is being referred to as "Applicant's allegedly admitted prior art." Applicant is not aware of any admitted prior art and requests that the examiner specify any such art and indicate if and how it is being relied upon in any subsequent rejection.

The instant obviousness rejection appears to be the identical or nearly identical to the rejection for anticipation over Goodman. As the obviousness rejection mentions no specific art to be combined with Goodman and raises no issues beyond those discussed under the rejection for anticipation, the examiner is referred to Applicant's rebuttal of Goodman under anticipation for Applicant's rebuttal under obviousness. It is respectfully submitted that Goodman is not enabling with respect to any pending claim and this deficiency is not remedied by any reference of record in the case.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is urged to contact the undersigned by telephone to address any outstanding issues standing in the way of an allowance.

Respectfully submitted,

Date: May 1, 2003

By _____

FOLEY & LARDNER
P.O. Box 80278
San Diego, California 92138-0278
Telephone: (858) 847-6700
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Barry S. Wilson
Attorney for Applicant
Registration No. 39,431

Antibodies produced in plants

A. Hiatt

Transgenic plant systems for the expression of mammalian antibodies offer opportunities for the study of plant metabolism and development. Agricultural production could provide virtually unlimited quantities of any antibody.

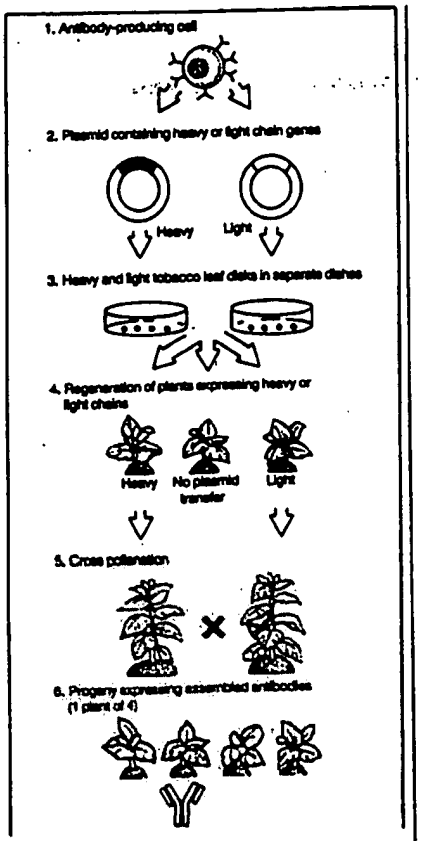
HETEROLOGOUS systems for the expression of mammalian antibodies will undoubtedly contribute a great deal towards our ability to isolate and manipulate immunoglobulins[1]. The latest heterologous host system for antibody synthesis is plants. Techniques to generate transgenic plants have been perfected to the point where a foreign protein can be targeted to an organ of choice as well as to subcellular compartments.

Production of antibodies by plant cells offers a variety of new possibilities for basic research in plant biology as well as for large-scale production of antibodies for use as therapeutic, diagnostic or affinity reagents. The unparalleled capacity and flexibility of agricultural production suggests that antibodies derived from plants may be significantly less expensive than antibodies from any other source. Moreover, antibodies in plants may become useful reagents for manipulating agronomic traits and possibly for ameliorating symptoms of pathogenic infections, as well as for isolating and processing environmental contaminants or industrial by-products.

Plant transformation

Successful expression of an antibody in tobacco has recently been reported[2]. A catalytic antibody[3] was chosen to test the ability of the tobacco cell to assemble and process immunoglobulin chains without compromising functionality. cDNAs encoding heavy and light chains were first inserted into *Agrobacterium tumefaciens*, a soil bacterium that has proven to be very useful for transforming many types of plant cells[4]. The *Agrobacterium* is responsible for transferring the DNA into the plant cell where it is subsequently integrated into the genome. Transformed plant cells are then regenerated to become mature plants[5].

The strategy used for antibody production was to transform tobacco leaf discs and regenerate separate plants expressing either the light or heavy chains (see figure). These plants were then sexually crossed to produce progeny-expressing functional antibody. Although the levels of expression varied widely, greater than one per cent of total protein constituted functional antibody in some plants. There is reason to believe that this level of expression can be augmented by using promoter elements capable of higher levels of transcription[6]. The antibody can easily be purified from homogenized leaves in one affinity purification step. The catalytic properties of the tobacco-produced antibody allow a precise evaluation of kinetic parameters such as K_m, K_i and K_{cat}; by these functional criteria, it is identical to the same antibody derived from hybridoma cells. Further characterization (for example, site of synthesis, secretion, glycosylation) will be reported elsewhere.



Production of antibodies in tobacco plants. Primary regenerants transformed with *Agrobacterium* containing heavy or light chain cDNAs are sexually crossed to enable assembly of a functional antibody in resulting progeny.

Of critical importance, is an evaluation of the immunogenicity of plant-derived antibodies in mammals. As plants do not contain sialyl transferase activity[7], the terminal residues of the carbohydrate on the heavy chain will be different from mammals. In all probability, they will consist of xylose, fucose, and/or *N*-acetylglucosamine[7]. The extent to which alterations in carbohydrate composition affect the biodistribution and serum clearance of the antibody remains to be determined.

Agricultural-scale production

Clearly, if antibodies are to be used for therapeutic purposes, techniques for large-scale production have to be developed. The high capacity and flexibility of agricultural production offers several advantages for obtaining antibodies: genetically stable seed stocks of antibody-producing plants can be isolated and stored indefinitely at low cost and the seed stock can be converted into a harvest of any quantity of antibody within one growing season.

Although tobacco has been used as the principle research tool to initiate the study of antibodies in plants, there may be more appropriate plants for production. A variety of common crop plants can be used as the production host. Acreages of perennial forage crops could be generated by clonal propagation or from seed and harvested numerous times in a growing season. The choice of species may depend on the quantity and nature of contaminants encountered during purification. Some candidates are alfalfa, soybean, tomato and potato.

As large-scale production of antibodies is not yet commonplace, appropriate techniques for the purification of hundreds or thousands of grams have yet to be perfected. The cost of agriculturally-produced antibodies is likely to be considerably less than antibodies produced from hybridoma cells or ascites fluid. For example, if antibodies were expressed in soybean and constituted one per cent of total protein in soybean meal, a kilogram of antibody could, hypothetically, be produced for less than $100 (US). This extrapolation is based on current costs for soybean production and does not take into account numerous hidden costs such as the cost of development and propagation of a sufficiently large and genetically characterized seed stock. In addition, the efficiency with which antibodies can be produced in specialized organs such as seeds or fruit is still not known.

Growth regulation

Plant growth and development is controlled by a limited number of low molecular weight hormones such as indoleacetic acid, ethylene, benzylaminopurine and a variety of more complex organic

molecules[9]. Little is known about the biosynthetic pathways or the mechanism of action of these hormones. However, by expression within the plant cell of monoclonal antibodies that recognise these hormones, it may be possible to evaluate developmental and metabolic events that are controlled by their free titre. Ideally, one would want to control the expression of the antibody as well as target expression to different organs or subcellular locations. In this way, activities of the hormone at various developmental stages could be unravelled.

Pathogen resistance

Antibodies against hormones are just one area where expression of an endogenous antibody could aid plant research. Another example is infection of plants by pathogens. Although many fungal, bacterial and viral pathogens have been characterized with respect to the genetics of host-pathogen interactions, very few have been thoroughly investigated at the biochemical level. In some instances, however, pathogen-related proteins or other organic molecules have been shown to be necessary for pathogenesis[9,10].

Expression of an intracellular antibody that binds antigens essential for pathogenesis may ameliorate the symptoms of the infection by reducing the functional titre. The advantage of this strategy is two-fold: first, it would not require isolation of genes involved in synthesis of the target antigen (as with anti-sense RNA expression); and second, pools of antigen which may be localized in subcellular compartments can be the specific target, leaving other pools unaffected. Clearly, the success of this approach will depend on a much more detailed understanding of the behaviour of antibodies in plants. Whereas antibodies have been successfully expressed intracellularly in both yeast and mammalian cells[11,12], attempts to assemble immunoglobulin chains in the cytosol of plants have been unsuccessful.

Current efforts are focusing on alternative methods which would by-pass the requirement for assembly of two immunoglobulin chains (for example, single chain antigen-binding constructs)[13]. In addition, attempts to localize an antigen-binding capacity to chloroplast and vacuole are in progress. Once we have a clear picture of the assembly, stability and functionality of targeted immunoglobulins, appropriate strategies for localized antigen binding can be devised.

Biofiltration

One of the key differences between plant cells and those of other organisms is the structure and characteristics of the surrounding cell wall. The mechanical strength and contiguous nature of plant cell walls is largely responsible for the rigidity of the entire plant. The diameter of pores in the cell wall imposes a restriction on the size of molecules that are freely permeable. This exclusion limit lies between 35 and 50 Å and corresponds to a molecular weight of less than 20,000 for a globular protein. Clearly, antibodies are too large to be freely permeable[14]. Consequently, expression of an antibody in a plant cell is equivalent to producing a binding and retention capacity within a semipermeable membrane. Any antigen with a molecular weight of less than 20,000 (for example, environmental pollutants, industrial by-products, pesticides and herbicides) might be collected and retained by a plant expressing an antibody that is functional *in situ*.

At present, research exploring the applications of biofilters is aimed at characterizing the functional properties of the antibody as it resides within the boundaries of the cell wall. Future efforts will be aimed at enhancing the functionality of antibodies in plants to enable catalytic processing of molecules retained within the cell.

Andrew Hiatt is a Molecular Biologist at the Research Institute of Scripps Clinic, La Jolla, California 92037, USA. For more information fill in reader service number 100.

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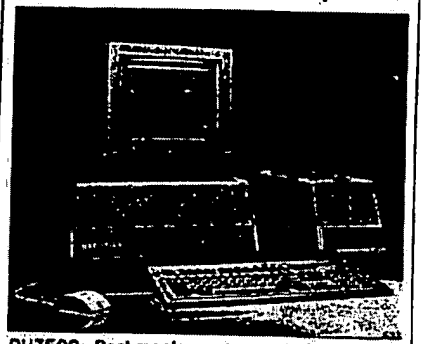
FASEB highlights

The Federation of American Societies for Experimental Biology (FASEB) annual meeting will be held in Washington, DC, next week. A micro-osmotic pump for slow-release drug delivery and a vertical tube gel apparatus will be among the many exhibits.

AT FASEB, Beckman Instruments will be launching the programmable DU7500 diode array UV/visible spectrophotometer designed for microvolume and ultra-microvolume samples of up to 100 µl (*Reader Service No. 101*). The patented



DU7500: Beckman's next generation of UV/visible spectrophotometers.

full spectrum quantitation applies all the data points in a scan to arrive at accurate and reliable component concentrations, says Beckman. Data are calculated using advanced vector quant maths. RediRead and RediScan modes allow the user to take readings or wavelength scans even when other measurements are in progress. A one-button prompt automatically sets up the new readings or scan, after which the interrupted research can be resumed. The DU7500 simplifies protein analysis by providing pre-selected parameters for Bradford (595 nm), Lowry (high sensitivity: 750 nm; low sensitivity: 500 nm), Biuret (540 nm) and direct UV method (280 nm). Kinetic analyses are run at single or multiple wavelengths: results can be displayed in five plot formats. Price for the DU7500, which will be in action in booth 1312, range from $15,000–25,000 (US), depending on configuration and choice of accessories.

To meet demands for an implantable micro-osmotic pump that can deliver a variety of bioactive compounds to animals weighing less than 10 grams, Alza Corporation has introduced the Alzet Model 1007D (*Reader Service No. 102*). Measuring just 17 mm in length and weighing 350 mg when empty, the Model 1007D provides the controlled administration of

Alza's micro-osmotic pumps provide sustained-release drug delivery.

WHAT IS CLAIMED IS:

1. A method for producing a mammalian peptide which comprises:

growing plant cells containing an integrated sequence comprising,

a first expression cassette having in the direction of transcription (1) a transcriptional and translational initiation region functional in said plant cells, (2) a structural gene coding for said mammalian peptide, and (3) a termination region,

whereby said structural gene is expressed to produce said mammalian peptide; and

isolating said mammalian peptide substantially free of plant cell components.

2. A method according to Claim 1, wherein said integrated sequence ~~includes~~ comprises a second expression cassette having in the direction of transcription (1) a transcriptional and translational initiation region functional in said plants, (2) a structural gene coding for a peptide which allows for selection of plant cells expressing said peptide, and (3) a termination region.

3. A method according to Claim 2, wherein said transcriptional and translational initiation region of said first expression cassette is derived at least in part from a transcriptional and translational initiation region of a Ti- or Ri-plasmid.

4. A method according to Claim 3, wherein said transcriptional and translational initiation region of said first expression cassette regulates expression of mannopine synthase, octopine synthase or nopaline synthase.

5. A method according to Claim 1, wherein said transcriptional and translational initiation

Exhibit 2

region of said first expression cassette regulates expression of a plant gene.

6. A method according to Claim 1, wherein said integrated sequence ~~includes~~ comprises a boundary region from T-DNA.

7. A method for producing an interferon which comprises:

growing plant cells containing an integrated sequence comprising,

a first expression cassette having in the direction of transcription (1) a transcriptional and translational initiation region functional in said plant cells and derived from a region which regulates expression of a T-DNA gene, (2) a structural gene coding for an interferon, and (3) a termination region functional in said plant cells,

whereby said structural gene is expressed to produce said interferon, and

isolating said interferon substantially free of plant cell components.

8. A method according to Claim 7, wherein said integrated sequence ~~includes~~ comprises a second expression cassette having in the direction of transcription (1) a transcriptional and translational initiation region functional in said plant cells, (2) a structural gene coding for an enzyme which imparts ~~re~~sistance, and (3) a T-DNA boundary.

9. A method according to Claim 8, wherein said first expression cassette transcriptional and translational initiation region regulates expression of the mannopine synthase gene of T-DNA.

10. An expression cassette comprising a DNA sequence having in the direction of transcription a transcriptional and translational initiation region functional in plant cells, a structural gene coding for a mammalian peptide, and a termination region functional in plant cells.

11. An expression cassette according to Claim 10 including joined to said DNA sequence a second expression cassette comprising a second transcriptional and translational initiation region functional in plant cells, a structural gene coding for a peptide providing a phenotypic property capable of selection in plant cells, and a termination region functional in plant cells.

12. An expression cassette according to Claim 11, ~~including~~ comprising a T-DNA boundary.

13. A DNA construct comprising a first expression cassette having in the direction of transcription a transcriptional and translational initiation region regulating the expression of mannopine synthase of T-DNA, a structural gene coding for γ-interferon and a termination region functional in plant cells, a second expression cassette comprising in the direction of transcription a transcriptional and translational initiation region regulatory the expression of octopine synthase of T-DNA, a structural gene coding for an enzyme imparting antibiotic resistance to plant cells, and a termination region functional in plant cells, and a T-DNA boundary.

8679-23 (pg 1 of 2)
ATTORNEY DOCKET NO.

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

MOLECULAR FARMING

the specification of which ☒ is attached hereto or ☐ was filed on _____ as Application Serial No. _____ and was amended on _____ (if applicable).

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a). I claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

COUNTRY	APPLICATION NUMBER	DATE OF FILING	PRIORITY CLAIMED UNDER 35 U.S.C. 119
			Yes____ No____
			Yes____ No____

I claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NO.	DATE OF FILING	STATUS
		☐ Patented ☐ Pending ☐ Abandoned
		☐ Patented ☐ Pending ☐ Abandoned

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) who are partners and associates in the firm of Townsend and Townsend to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

Bertram I. Rowland, Reg. No. 20,015 601
William M. Smith, Reg. No. 30,223
Stephen L. Hurst, Reg. No. 31,266

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202	FULL NAME OF INVENTOR	Last Name: KNAUF 402	First Name: Vic		Middle Name or Initial: C.
	RESIDENCE & CITIZENSHIP	City: Davis	State or Foreign Country: California		Country of Citizenship: U.S.A.
	POST OFFICE ADDRESS	Post Office Address: 2454 Elendil Lane	City: Davis	State or Country: California	Zip Code: 95616
203	FULL NAME OF INVENTOR	Last Name: HOUCK 403	First Name: Catherine		Middle Name or Initial: M.
	RESIDENCE & CITIZENSHIP	City: Vacaville	State or Foreign Country: California		Country of Citizenship: U.S.A.
	POST OFFICE ADDRESS	Post Office Address: 172 Carmel Court	City: Vacaville	State or Country: California	Zip Code: 95688

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 201	Signature of Inventor 202	Signature of Inventor 203
Date	Date	Date

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

MOLECULAR FARMING

the specification of which ☒ is attached hereto or ☐ was filed on _____ as Application Serial No. _____ and was amended on _____ (if applicable).

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a). I claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

COUNTRY	APPLICATION NUMBER	DATE OF FILING	PRIORITY CLAIMED UNDER 35 U.S.C. 119
			Yes____ No____
			Yes____ No____

I claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NO.	DATE OF FILING	STATUS
		☐ Patented ☐ Pending ☐ Abandoned
		☐ Patented ☐ Pending ☐ Abandoned

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) who are partners and associates in the firm of Townsend and Townsend to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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William M. Smith, Reg. No. 30,223
Stephen L. Hurst, Reg. No. 31,266

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201 FULL NAME OF INVENTOR	Last Name: COMAI	First Name: Luca		Middle Name or Initial:	
201 RESIDENCE & CITIZENSHIP	City: Davis	State or Foreign Country: California		Country of Citizenship: Italy	
201 POST OFFICE ADDRESS	Post Office Address: 1892 Sharon Avenue	City: Davis	State or Country: California		Zip Code: 95616
202 FULL NAME OF INVENTOR	Last Name:	First Name:		Middle Name or Initial:	
202 RESIDENCE & CITIZENSHIP	City:	State or Foreign Country:		Country of Citizenship:	
202 POST OFFICE ADDRESS	Post Office Address:	City:	State or Country:		Zip Code:
203 FULL NAME OF INVENTOR	Last Name:	First Name:		Middle Name or Initial:	
203 RESIDENCE & CITIZENSHIP	City:	State or Foreign Country:		Country of Citizenship:	
203 POST OFFICE ADDRESS	Post Office Address:	City:	State or Country:		Zip Code:

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 201	Signature of Inventor 202	Signature of Inventor 203
Date	Date	Date

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
06/760,236	07/29/85	GOODMAN	

BERTRAM I. ROWLAND
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EXAMINER	
FOXD	
ART UNIT	PAPER NUMBER
127	7

DATE MAILED: 06/09/87

This is a communication from the examiner in charge of your application.

COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 3/3/87 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-13 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☑ Claims 1-13 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings which are acceptable for examination purposes until such time as allowable subject matter is indicated.

8. ☐ Allowable subject matter having been indicated, formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. These drawings are ☐ acceptable; ☐ not acceptable (see explanation).

10. ☐ The ☐ proposed drawing correction and/or the ☐ proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved. ☐ disapproved (see explanation). However, the Patent and Trademark Office no longer makes drawing changes. It is now applicant's responsibility to ensure that the drawings are corrected. Corrections MUST be effected in accordance with the instructions set forth on the attached letter "INFORMATION ON HOW TO EFFECT DRAWING CHANGES", PTO-1474.

12. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

Exhibit 3

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an enabling disclosure.

The invention employs novel plasmids and microorganisms. Repeatability of the disclosed method and availability of starting materials is unclear; therefore a deposit should be made for enablement purpose.

Applicants may provide assurance of compliance with the requirements of §112 in the form of a declaration averring that (a) during the dependency of this application, access to the invention will be afforded to one determined by the Commissioner upon request, (b) all restrictions upon availibility to the public will be irrevocably removed upon granting of the patent and (c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer. See MPEP 608.01(p)C.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the above objection to the specification.

Claims 1-5, 7, 8, 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to Agrobacterium-mediated dicot transformation with chimeric genes comprising opine synthase promoters and structural genes encoding human interferon or antibiotic resistance as per pages 10-18. See MPEP 706.03(n) and 706.03(z).

The specification only provides detailed experimental examples demonstrating dicot transformation using Agrobacterium. Other means of plant transformation are limited by lack of chromosomal incorporation of DNA and lack of plant regeneration from transformed protoplasts. Agrobacterium-mediated transformation is limited by host range and regenerability of transformed protoplasts to the dicots (Goodman et al. pages 52-53). Undue experimentation would be required by one of ordinary skill in the art to obtain non-Agrobacterium mediated transfer of monocots as claimed in claims 1 and 7.

Furthermore, the specification only provides detailed experimental examples demonstrating the expression of human interferon in plant cells regulated by opine synthase promoters. As admitted by Applicants (page 5 of Amendment filed on February 23, 1987) the ability of a given promoter to direct translation of a detectable amount of stable, bioactive, recoverable gene product is not predictable. For example, phaseolin

expression was virtually undetectable in transformed sunflower cells under phaseolin promoter regulation but was detected at significantly higher levels when regulated by the octopine synthase promoter (Murai et al, page 480, third column, first full paragraph). Given the unpredictability inherent in the art, undue experimentation would be required by one of ordinary skill in the art to determine DNA sequences for non-disclosed mammalian peptides or promoters and to develop transformation vectors resulting in detectable expression of stable, bioactive peptides as claimed in claims 1-5, 8, 10 and 11.

Claims 1-4, 6-8, 12 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 7 are incomplete for failing to include the means of introducing the claimed integrated sequences into the plant cells. Claims 2, 6, 8 and 12 are indefinite in their recitation of "includes" or "including" as it is unclear whether this is an open or closed term. Claims 3 and 4 are confusing in their recitation of "said transcriptional and translational initiation region" for failing to distinguish between the regions of the first or second expression cassette.

Claims 3 and 7 are indefinite in their recitation of "derived ... from" which fails to adequately characterize the claimed regions. Claim 4 is indefinite for failing to employ proper Markush terminology. See MPEP 706.03y. Claim 13 is confusing in its recitation of "regulatory the expression of" as it is unclear what Applicants intend.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-4, 6-8 and 10-13 are rejected under 35 U.S.C. 103 as being unpatentable over Murai et al in view of Gray et al.

Murai et al. discloses the recovery of phaseolin from sunflower cells transformed with chimeric genes comprising structural genes encoding phaseolin and a

selectable antibiotic resistance enzyme regulated by octopine synthase promoters. Gray et al. discloses the recovery of biologically active human interferon from E. coli and monkey cells transformed with cDNA encoding interferon. In the absence of unexpected results it would be obvious to one of ordinary skill in the art to incorporate the interferon-encoding cDNA disclosed by Gray et al. into the plant transformation method disclosed by Murai et al to obtain the claimed methods and expression cassettes, since the disclosed plant transformation vectors and cDNA would continue to function in their known and expected manner.

Claim 5 is rejected under 35 U.S.C. 103 as being unpatentable over Murai et al in view of Gray et al as applied to claims 1-4, 6-8 and 10-13 above, and further in view of Herrera-Estella et al.

Murai et al taken in view of Gray et al discloses a method for recovering interferon from plants as discussed supra. Herrera-Estella et al. discloses plant transformation using the pea RUBISCO small subunit promoter to recover bacterial enzymes conferring antibiotic resistance. In the absence of unexpected results it would be obvious to one of ordinary skill in the art to incorporate the promoter disclosed by Herrera-Estrella et al. into the transformation method disclosed by Murai

et al taken in view of Gray et al, since the RUBISCO promoter would continue to function in its known and expected manner.

Claim 9 is rejected under 35 U.S.C. 103 as being unpatentable over Murai et al in view of Gray et al as applied to claims 1-4, 6-8 and 10-13 above, and further in view of Velten et al.

Murai et al taken in view of Gray et al discloses a method for recovering interferon from plants as discussed supra. Velten et al. discloses the use of the agropine (mannopine) promoter in plant transformation to recover bacterial enzymes encoding antibiotic resistance. In the absence of unexpected results it would be obvious to incorporate the promoter disclosed by Velten et al. into the transformation method disclosed by Murai et al taken in view of Gray et al. since each would continue to function in their known and expected manner.

Any inquiry concerning this communication should be directed to David T. Fox at telephone number 703-557-3920.

DTF

FOX:wdh

6/4/87

THOMAS G. WISEMAN
SUPERVISORY PATENT EXAMINER
ART UNIT 127

TO SEPARATE, O TOP AND BOTTOM EDGES, SNAP-APART AND ARD CARBON

FORM PTO-892 (REV. 3-78) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
NOTICE OF REFERENCES CITED	760,236	127	7
	APPLICANT(S) Goodman et al.		

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A						
	B						
	C						
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	F						
	G						
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FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

14	R	Velten et al. 1984. EMBO J 3(2): 2723-2730
14	S	Murai et al. 1983. Science 222: 476-482
14	T	Gray et al. 1982. Nature 295: 503-508
14	U	Goodman et al. 1987. Science 236: 48-54

EXAMINER	DATE
David T. Fox	5/23/87

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

TO SEPARATE,) TOP AND BOTTOM EDGES, SNAP-APART AND ARD CARBON

FORM PTO-892 (REV. 3-78) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
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	M								
	N								
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	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

R	Herrera-Estrella et al. 1984. Nature 310: 115-120
S	
T	
U	

EXAMINER	DATE
David T. Fox	5/23/87

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

Art Unit 184

MAILED

Paper No. 15

Appeal No. 89-0918

SEP 28 1989

vgb

ON BRIEF

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte Robert M. Goodman
Vic C. Knauf
Catherine M. Houck
and
Luca Comai

- - -

Application for Patent filed July 29, 1985, Serial No. 760,236. Mammalian Peptide Expression in Plant Cells.

Bertram I. Rowland et al. for appellants.

Supervisory Primary Examiner - Charles F. Warren.
Examiner - D. Fox.

Before Goldstein, W. Smith and Haight, Examiners-in-Chief.

Goldstein, Examiner-in-Chief.

This appeal is from the examiner's final rejection of claims 1 to 13. There are no allowed claims. Illustrative claims 1, 7 and 8 are reproduced below:

1. A method for producing a mammalian peptide which comprises:

growing plant cells containing an integrated sequence comprising,

a first expression cassette having in the direction of transcription (1) a transcriptional and translational initiation region functional in said plant cells, (2) a structural gene coding for said mammalian peptide, and (3) a termination region,

whereby said structural gene is expressed to produce said mammalian peptide; and

Exhibit 4

isolating said mammalian peptide substantially free of plant cell components.

7. A method for producing an interferon which comprises:

growing plant cells containing an integrated sequence comprising,

a first expression cassette having in the direction of transcription (1) a transcriptional and translational initiation region functional in said plant cells and derived from a region which regulates expression of a T-DNA gene, (2) a structural gene coding for an interferon, and (3) a termination region functional in said plant cells,

whereby said structural gene is expressed to produce said interferon, and

isolating said interferon substantially free of plant cell components.

8. A method according to Claim 7, wherein said plant cells are dicotyledon plant cells and said integrated sequence comprises a second expression cassette having in the direction of transcription (1) a transcriptional and translational initiation region functional in said plant cells, (2) a structural gene coding for an enzyme which imparts antibiotic resistance, and (3) a T-DNA boundary.

References relied upon by the examiner on appeal are:

Gray et al. (Gray), Nature, Vol. 295, February 1982, pages 503-508.

Murai et al. (Murai), Science, Vol. 222, November 1983, pages 476-482.

Herrera-Estrella et al. (Herrera-Estrella), Nature, Vol. 310, July 1984, pages 115-120.

Velten et al. (Velten), The EMBO Journal, Vol. 3, No. 12, 1984, pages 2723-2730.

Goodman et al. (Goodman), Science, Vol. 236, April 1987, pages 48-54.

Reference of record discussed in the following opinion:

Shaw et al. (Shaw), "A General Method for the Transfer of Cloned Genes to Plant Cells," Gene, Vol. 23, No. 3, 1983, pages 315-330.

All of the appealed claims have been finally rejected under either or both of 35 USC 103 and 112. There have been some clear errors in keeping track of which claims were subject to

exactly which grounds of rejection throughout the prosecution of this application. However, it is clear that these inadvertent errors have not clouded the issues, which have been clearly defined by both the examiner and appellants on the record. The claims which, in our view, correspond to the different grounds of rejection based on the correspondence of the claimed subject matter to the issues raised by the rejection in each case are as follows.

With respect to the rejection under 35 USC 103 for obviousness, claims 1 to 4, 6 to 8 and 10 to 12 have been rejected as being unpatentable over the combined teachings of Murai and Gray. Herrera-Estrella has been considered additionally with respect to claim 5, and Velten has been considered additionally with respect to claims 9 and 13. The situation with regard to the rejection over prior art is simplified by appellants' acknowledgement that patentability of all of the claims rests on the unobviousness of the broadest claims over the basic combination of Murai and Gray.

The basis of the rejection under 35 USC 112 for lack of an enabling disclosure is the failure to specify the mammalian gene to be expressed, the vector for its expression and (in the process claims) the host in which the vector operates. In the final rejection, all three of these criteria were considered together. In the answer on appeal, the examiner has stated two separate rejections, one limited to the specific gene and the other limited to the vector and host. Since we agree with the examiner's position with regard to all three limitations, we shall simply distinguish those claims which recite all three (or, in the case of the "construct" or "expression cassette" claims, the two relevant ones) from those which do not, i.e., we shall treat the two rejections as one, in the manner of the final rejection. Thus, the claims which are subject to the rejection under 35 USC 112,

because they do not recite all of the essential limitations, are claims 1 to 7 and 10 to 12. The claims which are free of this rejection are claims 8, 9 and 13. To illustrate this distinction, we have above reproduced claim 8 together with claim 7, from which it depends, and claim 1.

With respect to the rejection under 35 USC 103, we find appellants' arguments convincing of error on the part of the examiner. The state of the art illustrated on this entire record, including the discussion of the prior art in the original specification as filed, the references now relied on by the examiner and all of the additional references of record, is clearly such that motivation existed to do that which appellants have done and here claimed. The evidence also illustrates that success has been achieved in performing related but not identical biotechnological syntheses. A nonmammalian eukaryotic gene has been expressed in a plant cell (Murai). A mammalian gene has been expressed in a eukaryotic animal cell, but not a plant cell (Gray). However, the only report before us concerning the expression of a mammalian gene in cells of higher plants is the Shaw article, which reports the transfer of the mammalian gene to the plant genome but failure to obtain expression, which apparently failed at the transcription stage (see the last sentence of the summary).

The examiner has failed to indicate how, from the prior art evidence of record, one of ordinary skill in the relevant art would have known what modifications to make in the various prior art procedures to obtain a result different from that reported in the Shaw article for example. In the absence of such an explanation, we find that appellants' claims would not have been obvious under 35 USC 103 based on this record and the examiner's explication thereof.

We shall affirm the examiner's rejection of claims 1 to 7, and 10 to 12 under the first paragraph of 35 USC 112.

It appears to have been accepted by the examiner that the experimental portion of appellants' specification enables one of ordinary skill in the relevant art to repeat that which appellants have done, i.e., obtain the expression of an interferon gene through the use of a transformed Ti-plasmid in dicotyledonous plant cells. In view of the very same high order of unpredictability of success in extrapolating reported procedures to different systems, e.g., different genes, different vectors and different hosts, discussed above, appellants' arguments that their disclosure enables one of ordinary skill to practice the inventions claimed more generally in the broader claims without the exercise of undue experimentation are unreasonable on their face.

From the arguments presented by appellants in their brief on appeal, it appears that they have also taken the more extreme position that no amount of experimentation would be undue and that, having carried out one successful, specific biosynthesis, they are per se entitled to claim the entire concept disclosed as a research goal in the prior art of record.

The factors to be taken into consideration in determining whether or not the amount of experimentation required to practice the subject matter of a patent claim is unduly burdensome under 35 USC 112 have been discussed at great length in reported prior decisions. See, for example, Ex parte Forman, 230 USPQ 546 (BPAI 1986); Ex parte Jackson, 217 USPQ 804 (Bd. App. 1982). We shall not burden the present record with a repetition of that entire discussion here. It is amply clear from appellants' arguments that they have not taken cognizance of those factors. They have expressed their opinion that it is not necessary to enable one of ordinary skill in the relevant art "to avoid the expenditure of sweat and monies which applicants expended at a time

when they could not be certain of success" (brief on appeal, page 8) and that it is acceptable to require those of ordinary skill, in practicing the invention, "to carry out the peeling of onions, the cutting of meat and the preparing of stew in order to have the dinner" (brief on appeal, page 8). These statements are entirely antithetical to the policy expressed in the enablement requirement of 35 USC 112. In the present case, appellants have emphasized the "high degree of unpredictability of success" in modifying specific known procedures in this field (brief on appeal, page 21), and nowhere on this record can one find any indication of what specific modifications of the Shaw process, for example, were responsible for appellants' success relative to the incompletely satisfactory results obtained by Shaw. Thus, their position on the issue of undue experimentation is particularly untenable on this record.

The examiner's rejection of claims 1 to 7 and 10 to 12 is affirmed. The rejection of claims 8, 9 and 13 is reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR 1.136(a). See the final rule notice, 54 F.R. 29548 (July 13, 1989), 1105 O.G. 5 (August 1, 1989).

AFFIRMED-IN-PART

Melvin Goldstein)
Examiner-in-Chief)
)
)
William F. Smith) BOARD OF
Examiner-in-Chief) PATENT APPEALS
) AND
) INTERFERENCES
)
James C. Haight)
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